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(71) Applicant: **NOVADAQ TECHNOLOGIES INC.**
[CA/CA]; 3300 Highway #7, Suite 703, Concord, Ontario
L4K 4M3 (CA).

(72) Inventor: **FLOWER, Robert**; 11 Dellwood Court, Hunt-
valley, MD 21030 (US).

(74) Agent: **OGILVY RENAULT**; Attn: Mitchell, Robert,
Suite 1600, 1981 McGill College Avenue, Montreal,
Québec H3A 2Y3 (CA).

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(54) Title: **COMBINED PHOTOCOAGULATION AND PHOTODYNAMIC THERAPY**

(57) Abstract:

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**COMBINED PHOTOCOAGULATION
AND PHOTODYNAMIC THERAPY**

0001 This application claims priority from United States Patent Application No. 60/396146, filed July 17, 2002.

5 0002 This invention relates to a method for treating lesions, and more specifically where said lesion is an age related macular degeneration associated choroidal neovascularization, wherein said neovascularization is supplied by at least one blood vessel.

BACKGROUND OF THE INVENTION

10 0003 Lesions are normally defined as an abnormal tissue structure located in an organ or other body part, and are often a manifestation of a harmful condition, disease or illness. Lesions may take many specific forms, such as choroidal neovascularizations ("CNVs") which are found in the eye. In general, any abnormal vasculature in a body is a type of lesion.

15 0004 Lesions must often be identified and visualized prior to treatment and such methods are known in the art. For example, CNVs are routinely visualized using indocyanine green ("ICG") dye angiography ("ICGA"). It is based on use of the near-infrared fluorescent light wavelengths emitted by ICG, which readily penetrate the pigmented ocular tissues. Methods for enhancing visualization of CNVs (i.e. as taught in U.S. Patent No. 5,394,199) are also known in the art.

20 0005 Traditionally, CNVs were treated by destruction of the entire CNV membrane using photocoagulation. Photocoagulation involves the application of energy, such as through a laser, sufficient to reduce the flow of blood through a target vessel or tissue. Photocoagulation of an entire CNV, however, involved the destruction of a significant portion of the retina. Advances in the visualization of CNVs allowed for the ability to
25 perform high-speed imaging. This led to the development of a current AMD treatment modality, namely CNV feeder vessel photocoagulation treatment.

30 0006 Following visualization of a CNV feeder vessel (e.g. by ICGA), feeder vessel photocoagulation is performed by photocoagulating an afferent vessel supplying blood to a CNV. This reduces or stops the flow of blood to the CNV. With feeder vessel photocoagulation, an often smaller fundus area is photocoagulated since only the feeder

vessel is targeted even when the CNV itself may be relatively large in area. Also, the photocoagulation is often removed from the CNV, which may be juxta- or sub-foveal, thereby avoiding photocoagulation related damage to the fovea.

5 0007 One feeder vessel photocoagulation methodology also involves the use of a radiation absorbing dye, such as ICG. The presence of the radiation absorbing dye in a target blood vessel enhances the uptake of near-infrared laser energy and decreases the amount of laser energy required to photocoagulate the targeted vessel and is referred to as Dye-Enhanced Photocoagulation ("DEP"). Thus, DEP reduces the amount of concomitant damage to the overlying sensory retina.

10 0008 Another example of a current method for treating abnormal vasculature is photodynamic therapy ("PDT"). Generally, application of PDT requires administration of a photodynamic agent into a subject, typically by intra-venous injection. Once the agent arrives in a target site containing a tissue to be treated, the site is subjected to energy, e.g. light of a certain wavelength generated by a laser causing excitation of the agent. When the agent is
15 excited, it produces oxygen radicals which then attack the cells of the surrounding tissue, resulting in degradation of those cells. By way of example, and in the case of CNV, PDT destroys vascular endothelial cells of the CNV. This reduces, and preferably halts, the flow of blood within the CNV.

20 0009 It is possible that in some cases, reperfusion occurs following initially successful PDT of a CNV. PDT treatment may thus require multiple applications. Moreover, it now appears that the extent to which many PDT agents are selective for abnormal vasculature may not be as high as originally expected. In other words, concentration of PDT agent in the blood, rather than binding of PDT agent to the endothelium, is more determinative of efficacy of PDT treatment. As a result, the non-target areas of the fundus may be subjected to more PDT-
25 mediated damage than originally anticipated. Also, PDT therapy traditionally involves infusing the PDT agent into a subject's vasculature, typically over about a ten (10) minute period. Infusion requires large quantities of PDT agent. Large quantities of PDT agent also translate into an increase in the likelihood of side effects, higher total cost and more light sensitivity post-treatment.

30 0010 A need exists for improved methods of treatment of age-related macular degeneration associated choroidal neovascularizations and lesions generally.

SUMMARY OF THE INVENTION

0011 The present invention provides a more effective method for treating lesions, in an animal. The method of the present invention utilizes photocoagulation and PDT methodologies. One broad aspect of the inventive method contemplates treating a lesion by locating at least one vessel that supplies blood to the lesion, administering a treatment composition comprising a photodynamic agent to the subject, performing photocoagulation of said blood vessel to reduce the rate of blood flow through said blood vessel and thereby reduce the rate at which said treatment composition exits said lesion, and then performing PDT by exposing the lesion to radiation of an amount and type sufficient to activate the photodynamic agent and subject the lesion to PDT-mediated damage. In one embodiment of the invention, the method is used to treat AMD-related CNVs.

0012 Preferably, at least the partial presence of the PDT agent in the lesion is confirmed or approximated prior to photocoagulation of the feeder vessels. In one embodiment, this approximation or confirmation is carried out by administering a fluorescing dye and taking at least one angiogram.

0013 In another embodiment of the invention, a radiation absorbing dye is administered prior to photocoagulation of said blood vessel to improve said photocoagulation by using dye-enhanced photocoagulation.

0014 In a preferred embodiment of the invention, the photodynamic agent is administered along with a second dye that is both a fluorescing dye and a radiation absorbing dye, such as ICG, to treat AMD-related CNVs in a human.

0015 Also provided is a system for treating lesions implementing one preferred embodiment of the inventive method.

0016 One advantage of the present invention is that by cutting off the blood flow using photocoagulation or DEP after administration of the PDT agent, the PDT agent becomes incarcerated in the lesion. This is significant as PDT agents, such as Visudyne™, were previously thought to be held in the lesion during treatment because they were selectively bound to lesion tissues. However, it has come to light that PDT agents may not be as selectively bound to lesion tissues, such as CNVs, as originally anticipated. Therefore, by

cutting off the blood flow to the lesion, once it has become at least partially filled with PDT agent, the PDT agent is physically held in the lesion for and during PDT.

0017 A further advantage is that the incarceration of the PDT agent in the lesion also allows the PDT agent in non-lesion areas to be flushed out at higher flush-out rates as compared to
5 lesion areas. As a result, non-lesion areas will be subjected to less PDT mediated damage while maintaining PDT agent in the lesion area.

0018 A still further advantage is that the incarceration of PDT agent in the lesion increases the concentration of PDT agent in the lesion during treatment. A higher concentration of PDT agent in the lesion allows for more effective treatment.

10 0019 A still further advantage is that given that the PDT agent can be effectively concentrated in the lesion, the overall amounts of PDT agent used can be lowered. In the instance where PDT agent is infused, infusion time can therefore be correspondingly lowered. This is economically advantageous and decreases the likelihood of side effects resulting from the PDT agent.

15 0020 A still further advantage is that the reduction of blood flow through the feeder vessel enhances the rate of PDT-induced clot formation during PDT by reducing the movement and flow of blood through the lesion.

0021 A still further advantage is that, in the case of AMD-related CNV, post-PDT sensitivity to sunlight is significantly greatly reduced because of greatly reduced quantities of
20 administered PDT agent.

BRIEF DESCRIPTION OF THE DRAWINGS

0022 Figure 1 illustrates, in flow chart form, a method for treating a lesion.

0023 Figure 2 illustrates an overall system diagram implementing one embodiment of the inventive method.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

0024 In the following description, numerous specific details are set forth to provide a thorough understanding of the invention. However, it is understood that the invention may be

practiced without these specific details. In other instances, well-known processes have not been described or shown in detail in order not to obscure the invention.

0025 The methods of the present invention are claimed and described herein as a series of treatment steps. It should be understood that these methods and associated steps may be performed in any logical order that preserves the spirit of the invention. Moreover, the methods may be performed alone, or in conjunction with other procedures and treatments administered before, during or after such methods and steps set forth herein without departing from the scope and spirit of the invention. Further, it is contemplated that the term animals as used herein includes, but is not limited to, humans.

0026 Achieving even more effective treatment of lesions, such as AMD-related CNV, lies in combining photocoagulation (or DEP) with PDT treatment methodologies.

0027 Referring to Figure 1, a method for treating lesions according to one broad aspect of the invention is shown 10. The lesion should further have a blood vessel that carries blood into the lesion. The method 10 includes the following steps. Locating a feeder vessel associated with a lesion 11. Administering a composition comprising a photodynamic agent to the animal to fill at least a portion of the lesion with the composition 12. Energy, such as a first treatment light is then applied to the feeder vessel, of sufficient type and amount to photocoagulate the feeder vessel thereby reducing the rate of blood flow in the feeder vessel and decreasing the rate at which the composition exits the lesion 13. PDT is then performed by exposing the lesion to energy, such as a second treatment light, of a type and amount sufficient to excite the photodynamic dye 14. Reducing, including stopping all together, the rate at which the composition, containing the PDT agent, exits a lesion is also referred to as "incarcerating", "holding", "maintaining", "sequestering" or "trapping" the PDT agent in the lesion. Further, it is understood that when referring to incarcerating the composition in the lesion, it is not necessary that all of the administered composition be incarcerated, but merely a proportion thereof.

0028 In a preferred embodiment of the invention, the inventive method is used to treat AMD related CNVs.

0029 In one embodiment of the invention, locating a feeder vessel of a lesion 11 is accomplished by administering a fluorescent dye to an animal, applying energy of a type and amount sufficient to cause said dye to fluoresce, and obtaining at least one angiogram of a

pre-selected area of interest containing the lesion. In a further embodiment of the invention, a CNV and its associated feeder vessels are visualized using Indocyanine Green Dye Fluorescence Angiography. ICG dye is administered to a subject intravenously and allowed to perfuse through the subject's vasculature. Visualization is preferably effected by irradiating a pre-selected area, containing the CNV, with a laser light of a type and in an amount sufficient to cause the ICG dye to fluoresce.

0030 A preferred dosage of ICG, for visualizing CNV feeder vessels, is about 7.5 mg administered at a concentration of about 25mg/ml in a volume of approximately 0.3ml administered intravenously. Only one bolus is required per imaging sequence but multiple boluses may be employed. A concentration of about 0.025mg/ml in blood theoretically produces the most fluorescence from the fundus of a mammalian eye. Additionally, in some embodiments of the invention, administration of ICG intravenously is followed by a 5ml saline flush. The saline flush is used to rapidly push the bolus out of the cubital vein and into the thoracic cavity.

0031 Activation of ICG dye is preferably effected using a laser light source in the range of about 780nm-830nm. When visualizing a CNV and its associated feeder vessels in a mammalian eye, laser light used to excite dye fluorescence preferably irradiates a target site of about 1cm². Irradiation is preferably effected by irradiating the target area for about 10-20 seconds with a 1-4 ms pulse every 40 ms, each pulse having a peak power of about 300mW to 700mW. Typically, about 10mW to 40mW of average power is used.

0032 Capturing images of the fluorescing vasculature can be accomplished by numerous means which are known and will be apparent to a person skilled in the art. Images are preferably captured as high speed angiographic images on a CCD camera. The resultant images are analyzed to identify a lesion and feeder vessels associated with that lesion.

0033 While the above represents preferred parameters for visualizing a CNV and identifying associated feeder vessels, it is well known in the art that other dosages are also effective to produce fluorescence in the eye such that a CNV and its associated feeder vessels can be identified and located.

0034 Following the locating of a feeder vessel associated with a lesion, a composition comprising a photodynamic dye is administered to the subject. The photodynamic dye can be one or a combination of any of a number of available photodynamic agents. The agent

selected should be capable of causing damage to a targeted tissue after exposure to an appropriate type of radiation, e.g. light of a certain wavelength, typically between about 630nm and about 750nm. Many dyes that meet these criteria are available, and include, but are not limited to the following dyes, some of which are enumerated in U.S. Patent No.

5 6,443,976:

hematoporphyrins, which include derivatives thereof such as, e.g. dihematoporphyrins ethers and dimer and trimers of hematoporphyrins (examples of which are described in U.S. Patent Nos. 4,968,715 and 5,190,966), and improvements thereon, examples of the latter being described in U.S. Patent Nos. 5,028,621, 4,866,168, 4,649,151 and
10 5,438,071;

aminolevulinic acids (precursors to hematoporphyrin) as sources of photodynamic compounds, as described and exemplified in U.S. Patent No. 5,079,262;

porphyrins, including boronated porphyrin, benzoporphyrin, and derivatives thereof, and as further exemplified by the green porphyrin described in U.S. Patent Nos.
15 4,883,790, 4,920,143, 5,095,030 and 5,171,749;

merocyanines;

porphycenes;

porfimer sodium;

indocyanine green

20 verteporfin (Visudyne™, CIBA Vision);

Photofrin II™;

PH-10™;

chlorins, as exemplified by meso-tetra(hydroxyphenyl)-chlorin and bacteriochlorins, the latter exemplified in U.S. Patent Nos. 5,171,741, 5,173,504;

25 zinc phthalocyanine, as described in U.S. Patent No. 5,166,197;

purpurins, such as tin ethyl etiopurpurin (SnET2™, Miravant);

pheophorbides, examples of which are described in U.S. Patent Nos. 5,198,460, 5,002,962 and 5,093,349; and

monoclonal antibody-dye conjugates of each of the foregoing.

0035 In one preferred embodiment, Visudyne™ is used as the photodynamic agent when
5 treating a CNV in a human or mammalian eye. In some embodiments of the invention, the photodynamic agent is administered along with a pharmaceutically acceptable carrier.

0036 The dose of photodynamic dye to be administered is that amount sufficient to, upon
excitation, damage a specific target tissue. Given the various acceptable ways that a
photodynamic agent can be administered to a subject, including, but not limited to delivery
10 via liposomes or intravenous injection, a dosage will vary accordingly. A preferred dosage of photodynamic agent will therefore depend on mode of delivery, type of agent, and composition.

0037 In one embodiment of the invention, 15mg of Visudyne™ is diluted in 7.5ml to
produce a 2mg/ml solution. Dose for a subject is then calculated on the basis of surface area
15 of 6mg/m². Based on this, the appropriate amount is extracted from Visudyne™ solution and is diluted to 30ml with 5% dextrose solution. The 30ml of Visudyne™ solution is then infused over 8 minutes into the subject's vasculature.

0038 In another embodiment of the invention, the photodynamic agent is delivered as a
rapid bolus intravenously. Additionally, in this embodiment of the invention, administration
20 of PDT agent is followed by a 5ml saline flush. The saline flush is used to rapidly push the bolus out of the cubital vein and into the thoracic cavity.

0039 In one preferred embodiment of the invention, after administering the PDT agent but
prior to photocoagulation of the feeder vessel, at least the partial presence of the PDT agent
in the lesion is confirmed or at least approximated. This can be achieved by administering a
25 fluorescing dye separately or along with the photodynamic agent but prior to photocoagulation of the feeder vessel. Such dye is effective for fluorescence angiography and includes, but is not limited to, ICG. Energy sufficient to fluoresce the dye is applied and at least one angiographic image is then captured.

0040 If the fluorescing dye is administered along with the PDT agent in the same treatment composition (i.e. as part of the same bolus or infusion mixture), then subsequent fluorescent angiography will show the presence of that bolus or mixture (and thus the PDT agent) in the lesion as indicated by fluorescence within said lesion. If the fluorescing dye is administered separately from the PDT agent, the presence of the PDT agent in the lesion can also be approximated by calculating the arrival of the PDT agent in the lesion depending on the pre-determined time lapse between the administration of the PDT agent and fluorescing dye.

0041 In another preferred embodiment of the invention, a radiation absorbing dye is prior to photocoagulation of the feeder vessel. Such dye is effective for dye-enhanced photocoagulation and includes, but is not limited to, ICG. The radiation absorbing dye can be administered separately or along with the photodynamic agent.

0042 In treating CNVs, Visudyne™ is preferably combined with ICG dye such that a 0.3ml formulation has final concentration of about 65mg/ml ICG. Intravenous administration of the bolus is followed by a 5ml saline flush. Advantageously, ICG is both a fluorescing and radiation-absorbing dye. By irradiating the fundus of the eye with radiation sufficient to fluoresce the ICG dye, the practitioner can approximate or confirm the presence of the combined ICG/PDT agent formulation in the CNV while ICG also being effective for subsequent DEP. While these represent preferred values for a combined Visudyne™ and ICG bolus, it will be understood by those skilled in the art that other values are permissible and effective.

0043 Following administration of a photodynamic agent such that the lesion is at least partially filled with an effective amount of photodynamic agent, photocoagulation of the feeder vessel of the lesion is performed. Targeting of a photocoagulation treatment beam is based upon information previously derived from the locating of the feeder vessel associated with the lesion. Photocoagulation is effected by applying radiation of a kind and amount sufficient to effect an occlusion of a target feeder vessel. It is believed that such occlusion occurs by increasing the temperature of the feeder vessel, resulting in either cauterization of the feeder vessel or clotting of the blood within the feeder vessel. As a result, the rate of blood flow through the feeder vessel is reduced. Photocoagulation of a vessel results in the reduction in the rate of blood flow through such vessel, this includes but is not limited to halting blood flow completely.

0044 In embodiments of the invention where a radiation absorbing dye is administered, enhanced photocoagulation of the feeder vessel is effected by utilizing DEP. In the preferred embodiment wherein a combined bolus of ICG dye and Visudyne™ is administered, photocoagulation is enhanced by utilizing the radiation absorbing properties of the ICG dye to perform DEP of the feeder vessel. Thus, in this embodiment, ICG can act as both the fluorescing dye and the radiation-absorbing dye. Preferably, an approximately 810nm treatment laser is used at about 400-600mW for about 1.0-1.5 seconds to effect ICG DEP. This produces about 0.4J-0.9J of energy sufficient to photocoagulate the vessel in the presence of ICG.

0045 By photocoagulating a feeder vessel that supplies blood into a lesion just after the photodynamic agent has at least partially filled the lesion, the photodynamic agent is incarcerated in the lesion since the rate of fluid flow through the feeder vessel is reduced and thus the rate at which the PDT agent exits the lesion is also reduced.

0046 ICG is known to also have some photodynamic properties. Thus, in some embodiments of the invention, ICG is used as a photodynamic agent, fluorescing dye and a radiation-absorbing dye.

0047 The photodynamic agent, fluorescing dye and the radiation-absorbing dye may each be delivered separately as rapid boluses intravenously, as a rapid single bolus, each infused over a defined period of time, or any combination thereof without departing from the spirit of the invention.

0048 Photodynamic therapy is then performed on the lesion 14. The target tissue is irradiated with radiation of a type and amount sufficient to excite the PDT agent and damage the lesion. Thus, the radiation excites the PDT agent, now incarcerated in the lesion, effecting PDT treatment of the lesion.

0049 In one embodiment of the invention, after photocoagulation of the feeder vessel but prior to PDT, there is an additional step of confirming that the rate at which PDT exits the lesion has been reduced. In those embodiments where a fluorescing dye was administered along with the PDT agent, this confirmation can be achieved by applying energy to the area of the lesion and obtaining a subsequent angiographic image. If the PDT agent/fluorescing dye mixture is incarcerated in the lesion, vessels outside of the lesion will be subjected to regular flush out rates. Thus, the angiographic image will show fluorescence for vessels

within the lesion with a marked decrease in fluorescence in vessels outside the lesion. In those embodiments where no fluorescing dye was administered prior to photocoagulation, then confirmation can be achieved by first administering a fluorescing dye before applying the appropriate energy to fluoresce the dye and obtaining a subsequent angiographic image.

5 In this case, since the feeder vessel has been photocoagulated, the newly administered fluorescing dye will not be able to enter the lesion (or at least enter at a reduced rate). Thus, the angiographic image will show fluorescence for vessels outside the lesion with a marked decrease in fluorescence in vessels within the lesion.

10 0050 Typical parameters for photocoagulation, DEP and PDT have been provided as preferred values and should not be construed as a limitation on the claims of the present invention. It will be apparent to those skilled in the art that other parameters are permissible and effective to work the invention.

15 0051 A lesion is therefore attacked on two fronts. First, the lesion's blood supply is cut off using photocoagulation or DEP. This has the effect of starving the lesion and immediately reducing the hemodynamic pressure. Second, the abnormal vasculature itself is targeted by PDT. Excitation of the photodynamic agent present in the lesion additionally damages the lesion directly.

20 0052 This combined photocoagulation (preferably DEP)/PDT is not a simple serial application of both PDT and DEP, but an integrated method. This integrated method, consisting of PDT and DEP methodologies in a predetermined order has new and unanticipated results, when compared to PDT and DEP performed separately.

25 0053 Photocoagulation is performed after at least one feeder vessel associated with a lesion has been identified and a photodynamic agent has been administered, but before application of PDT treatment radiation. Only after photocoagulation of the feeder vessel is the PDT radiation applied to a predetermined treatment area containing the lesion to effect activation of the PDT agent.

0054 Significantly, the present invention of combined photocoagulation and PDT as outlined has several advantageous effects over and above the additive effect of the individual therapies alone. As outlined, this combined therapy exhibits advantageous synergistic effects.

0055 Referring to figure 2, a system 200 is provided for implementing one preferred embodiment of the inventive method. A tool for administering a composition intravenously such as a syringe 231 is provided. A lesion 211 is supplied by a feeder vessel 210, both shown magnified. A CCD camera 220 is provided. A computer system 226 comprises a CPU 222, memory 221, such as a hard disk and random access memory, an imaging processor 223, a PC monitor 224 and one or more input devices 225. A controller 227 is provided. A first laser 230, a second laser 229 and a third laser 228 are provided.

0056 In practice, the identification of the feeder vessel 210 is carried out by injecting a patient intravenously with a fluorescent dye, preferably ICG, using the syringe 231. Energy, of a type and amount sufficient to cause the fluorescent dye in the blood vessels, in and around the lesion 211, to fluoresce, is applied using the first laser 230. The first laser 230 is controlled by the controller 227 that receives input signals from the CPU 222. At least one angiographic image, of the fluorescing lesion 211 and the surrounding area, is then taken using the CCD camera 220. Said angiographic image is stored in memory 221 and displayed on the monitor 224 using an imaging processor 223, thus allowing a feeder vessel 210 to be identified.

0057 A treatment composition, comprising a PDT agent and ICG dye is then administered intravenously using a syringe 231. The presence of the treatment composition in the area corresponding to the lesion 211 and the feeder vessel 210, is confirmed by applying energy, using the first laser, of a type and amount sufficient to cause the ICG in the blood vessels of the lesion 211 and the feeder vessel 210 to fluoresce. An angiographic image is then taken using the CCD camera 220 and displayed on the monitor 224 as described above.

0058 The feeder vessel 210 is then photocoagulated by applying energy, of a type and amount sufficient to reduce the rate of blood flow through said feeder vessel 210, using the second laser 229. The second laser 229 is controlled by the controller 227 which receives input signals from the CPU 222.

0059 The lesion 211 is then subjected to PDT by applying energy, of a type and amount sufficient to excite said PDT agent, using the third laser 228. The third laser 228 is controlled by the controller 227 which receives input signals from the CPU 222.

0060 Although the invention has been described with reference to certain specific embodiments, various modifications thereof will be apparent to those skilled in the art

without departing from the spirit and scope of the invention as outlined in the claims
appended hereto.

**THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:**

- 5 1. A method for treating a lesion in an animal, said animal having at least one blood vessel that carries blood to said lesion, comprising:
 - (i) locating said blood vessel;
 - (ii) administering a treatment composition comprising a photodynamic agent suitable for photodynamic therapy;
 - 10 (iii) applying energy to said blood vessel, of a type and an amount sufficient to reduce the rate of blood flow through said blood vessel and thereby reduce the rate at which said treatment composition exits said lesion; and
 - (iv) applying energy to said lesion, of a type and an amount sufficient to excite said photodynamic agent.
- 15 2. The method according to claim 1, wherein said lesion is an age related macular degeneration associated choroidal neovascularization in a human.
3. The method according to claim 1, wherein said photodynamic agent is indocyanine green dye.
4. The method according to claim 1, wherein said treatment composition is administered intravenously as a rapid bolus.
- 20 5. The method according to claim 4, wherein said intravenous administration of said treatment composition is followed by intravenously administering a saline flush.
6. The method according to claim 1, wherein said treatment composition is administered by intravenously infusing said treatment composition over a predefined time interval.
- 25 7. The method according to claim 1, wherein step (iii) is performed after a pre-defined time interval following step (ii).
8. The method according to claim 1, wherein the application of energy to said blood vessel in step (iii) halts the blood flow through said blood vessel and thereby halting the rate at which said treatment composition in said lesion.
9. The method according to claim 1, wherein said treatment composition is administered using a heat-sensitive liposome.
- 30 10. The method according to claim 1, wherein said locating of said blood vessel is carried out using fluorescent dye angiography comprising:
 - (a) administering a visualizing composition comprising a fluorescing dye;

- (b) applying energy of a type and in an amount sufficient to cause said fluorescing dye to fluoresce as said fluorescing dye flows through the blood vessels located within a pre-selected area containing said blood vessel;
- (c) obtaining at least one angiographic image of the fluorescing dye in the blood vessels located within said preselected area sufficient to locate said blood vessel that carries blood into said lesion.
11. The method according to claim 10, wherein said fluorescent dye is indocyanine green dye.
12. The method according to claim 1, wherein prior to step (iii), there is an additional step of approximating or confirming that the lesion is at least partially filled with said treatment composition.
13. The method according to claim 12 wherein said approximating or confirming that said lesion is at least partially filled with said treatment composition, comprises:
- (a) administering a fluorescing dye;
- (b) applying energy of a type and in an amount sufficient to cause said fluorescing dye to fluoresce as said fluorescing dye flows through the blood vessels comprising said lesion; and
- (c) obtaining at least one angiographic image of the fluorescing dye in the blood vessels comprising the lesion.
14. The method according to claim 13, wherein said administering of fluorescing dye is achieved by said fluorescing dye forming part of said treatment composition.
15. The method according to claim 13, wherein said fluorescent dye is indocyanine green dye.
16. The method according to claim 1, wherein:
- (a) prior to step (iii), there is an additional step of administering a radiation absorbing dye suitable for dye-enhanced photocoagulation; and
- (b) thereby step (iii) results in dye enhanced photocoagulation of said blood vessel.
17. The method according to claim 16, wherein said administering of radiation absorbing dye is achieved by said radiation absorbing dye forming part of said treatment composition.
18. The method according to claim 16, wherein said radiation absorbing dye is indocyanine green dye.
19. The method according to claim 1, wherein:
- (a) prior to step (iii), there is an additional step of administering a radiation absorbing dye suitable for dye-enhanced photocoagulation;

- (b) thereby step (iii) results in dye enhanced photocoagulation of said blood vessel;
- (c) prior to step (iii), there is another additional step of approximating or confirming that the lesion is at least partially filled with said treatment composition; and
- (d) said confirming that said lesion is at least partially filled with said treatment composition comprises:
- (I) administering a fluorescing dye;
 - (II) applying energy of a type and in an amount sufficient to cause said fluorescing dye to fluoresce as said fluorescing dye flows through the blood vessels comprising said lesion; and
 - (III) obtaining at least one angiographic image of the fluorescing dye in the blood vessels comprising the lesion.

20. The method according to claim 19, wherein said administering of fluorescing dye and administering of radiation absorbing dye are achieved by said fluorescing dye and said radiation absorbing dye forming part of said treatment composition.

21. The method according to claim 19, wherein said fluorescing dye and said radiation absorbing dye are indocyanine green dye.

22. The method according to claim 1, wherein after step (iii) but prior to step (iv), there is an additional step of confirming that the rate at which said treatment composition exits said lesion has been reduced.

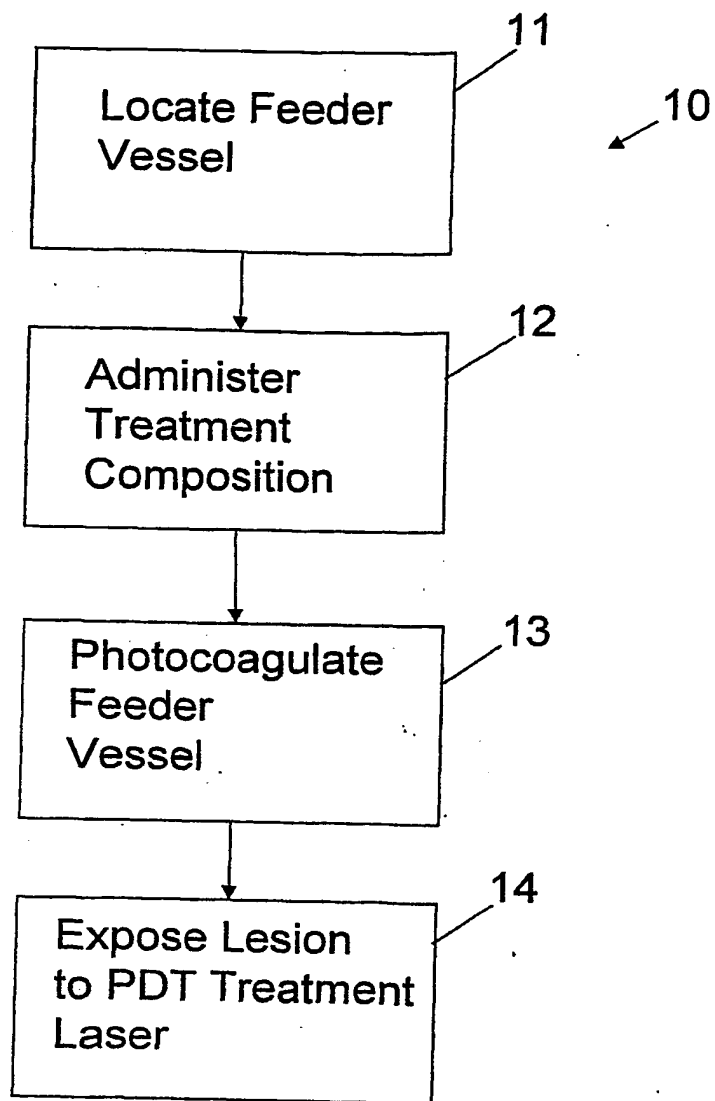
23. The method according to claim 22, wherein said confirming that the rate at which said treatment composition exits said lesion has been reduced, comprises:

- (a) administering a fluorescing dye;
- (b) applying energy of a type and in an amount sufficient to cause said fluorescing dye to fluoresce as said fluorescing dye flows through the blood vessels comprising said lesion; and
- (c) obtaining at least one angiographic image of said fluorescing dye in the blood vessels comprising the lesion.

24. The method according to claim 13, wherein after step (iii) but prior to step (iv), there is an additional step of confirming that the rate at which said treatment composition exits said lesion has been reduced.

25. The method according to claim 24, wherein said confirming that the rate at which said treatment composition exits said lesion has been reduced, comprises:

- (a) obtaining at least one angiographic image of said fluorescing dye in the blood vessels comprising the lesion.

**Figure 1**

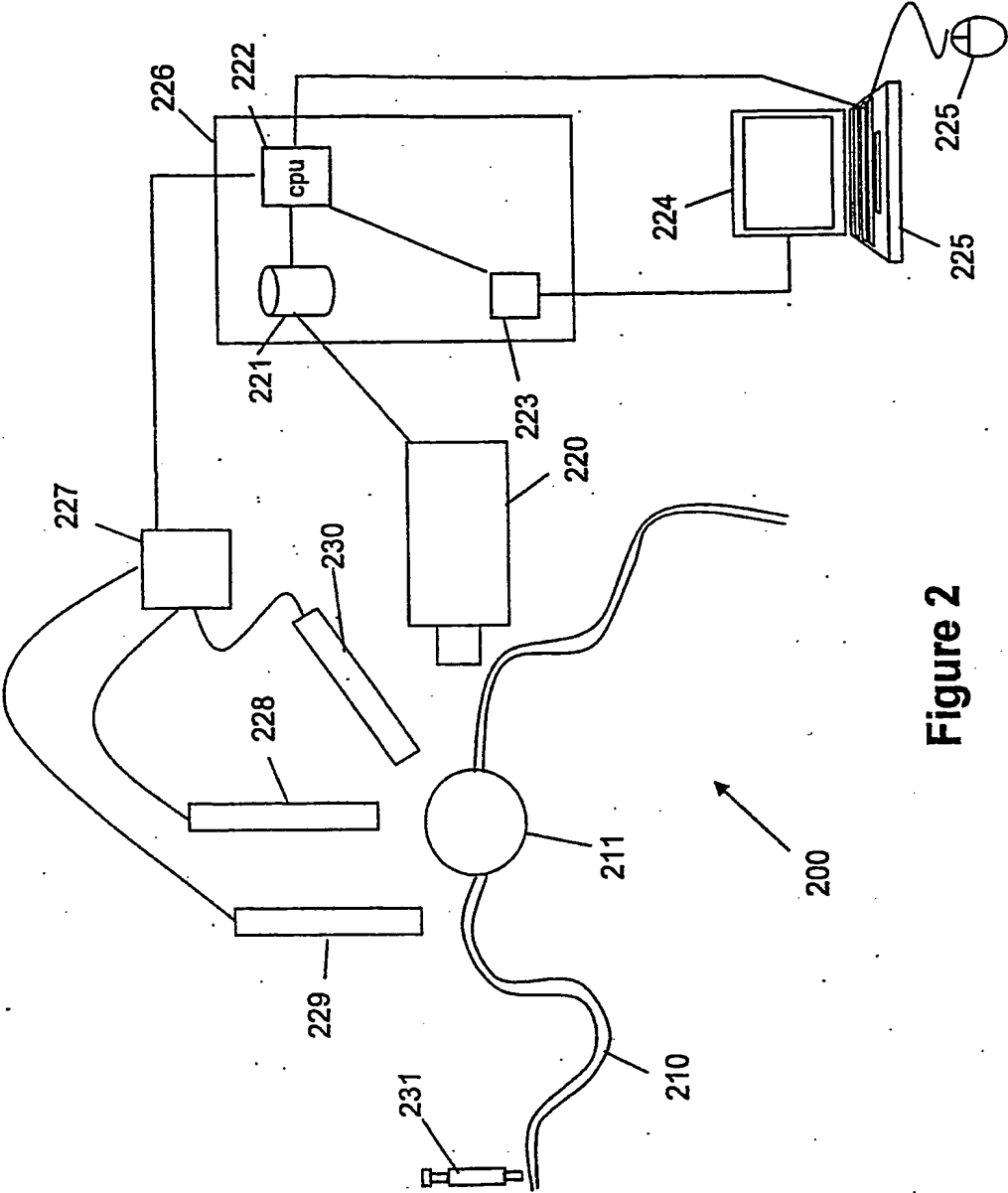


Figure 2

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT WIPO

(PCT Article 17(2)(a), Rules 13ter.1(c) and Rule 39)

Applicant's or agent's file reference 16336-18PCT	IMPORTANT DECLARATION	Date of mailing(day/month/year) 09/10/2003
International application No. PCT/CA 03/ 01071	International filing date(day/month/year) 16/07/2003	(Earliest) Priority date(day/month/year) 17/07/2002
International Patent Classification (IPC) or both national classification and IPC A61F9/008		
Applicant NOVADAQ TECHNOLOGIES INC.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that no international search report will be established on the international application for the reasons indicated below


1. ☒ The subject matter of the international application relates to:
 - a. ☐ scientific theories.
 - b. ☐ mathematical theories
 - c. ☐ plant varieties.
 - d. ☐ animal varieties.
 - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
 - f. ☐ schemes, rules or methods of doing business.
 - g. ☐ schemes, rules or methods of performing purely mental acts.
 - h. ☐ schemes, rules or methods of playing games.
 - i. ☒ methods for treatment of the human body by surgery or therapy.
 - j. ☒ methods for treatment of the animal body by surgery or therapy.
 - k. ☐ diagnostic methods practised on the human or animal body.
 - l. ☐ mere presentations of information.
 - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.
2. ☐ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

☐ the description
 ☐ the claims
 ☐ the drawings
3. ☐ The failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions prevents a meaningful search from being carried out:

☐ the written form has not been furnished or does not comply with the standard.
 ☐ the computer readable form has not been furnished or does not comply with the standard.
4. Further comments:

see further information continued from PCT/ISA 203

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Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Johannes Van Brummelen
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

All claims are directed to a method for treatment of the human or animal body by therapy and/or surgery - Rule 39.1(iv) PCT. Therefore, the International Search Authority is not required to carry out a search for those claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

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